Zagazig J. Pharm. Sci., June 2000
Vol. 9 , No. 1, pp. 9 -16

ISSN 1110 -5089

SYNTHESIS OF NEW NONCLASSICAL DIBENZODIAZEPINE DERIVATIVES AS POTENTIAL ANTIPSYCHOTIC AGENTS

Osama I.El-Sabbagh and Abd-El Alim F. Abd-El Alim*

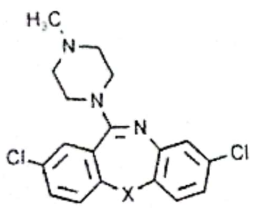
Depart. of Medicinal Chemistry, Faculty of Pharmacy, Zagazig University, Zagazig, Egypt.
*Depart. of Phamacology, Faculty of Vet. Medicine, Zagazig University, Zagazig, Egypt.

ABSTRACT

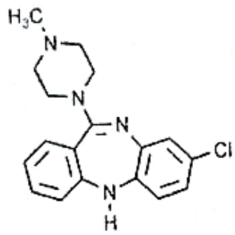
Two series of 8-chloro-2, 3, 4, 5,10,11-hexahydro-11-substituted-1H-dibenzo[b,e] [1,4] diazepine-1-ones and their 3,3-dimethyl analogs were prepared via internal Mannich reaction of 3-[(2- amino-4- chlorophenyl) amino] -2-cyclohexen-1-one and its 5,5-dimethyl analog, respectively, with different aldehydes at room temperature. The synthesized compounds were evaluated for their clozapine-like properties. The structures of the novel compounds were confirmed using elemental analyses and different spectroscopic methods. Pharmacological evaluation of some of the synthesized dibenzodiazepine derivatives revealed that compounds 4 and 17 (having 4-bromophenyl moiety) exhibited a high antipsychotic and sedative properties.

INTRODUCTION

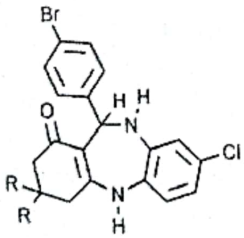
Dibenzoazepines represent a valuable class of antipsychoic drugs[1] . Some compounds of this class are known to be typical neuroleptic agents e.g. loxapine (I), clothiapine (II) and isoclozapine (III) while others are atypical[1-3] e.g. clozapine (IV). It is known that clozapine possesses antimuscarinic, antiserotonergic, sedative and weak antidopaminergic properties[4,5]. Although the use of atypical clozapine in treatment of schizophrenia[6-9] avoided the main disadvantage of typical ones e.g. extrapyrimidal side effects, still its use is limited due to the ability to induce agranulocytosis and other side effects [10-12] .



I X = O Loxapine
II X = S Clothiapine
III X = NH Isoclozapine



IV Clozapine

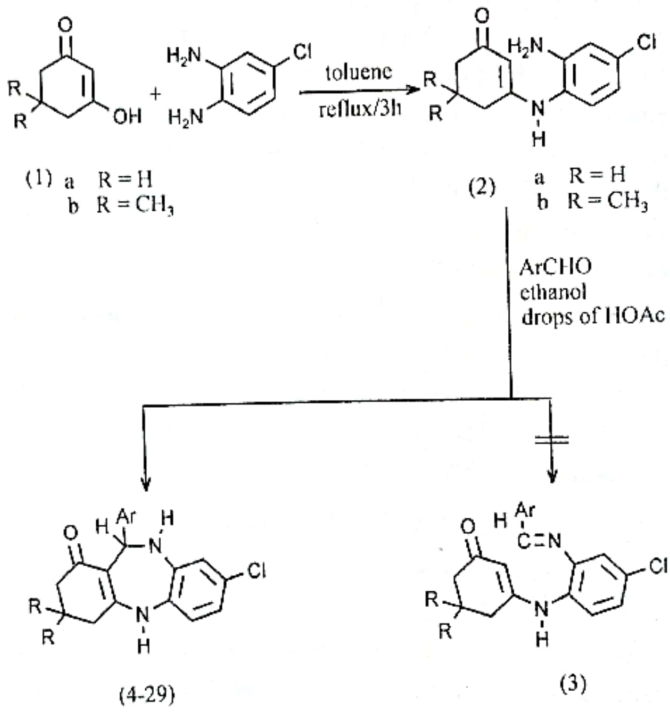


4 R = H
17 R = CH_3

The aim of the present study is the synthesis of new clozapine-like antipsychotic agents with lower side effects.

CHEMISTRY

In this article, new nonclassical dibenzodiazepine derivatives were synthesized as shown in scheme (A).



(1) a R = H, b R = CH_3 (2) a R = H, b R = CH_3 (4-29) (3)

Scheme (A)

In the present work, two new enaminones (2a and 2b) were synthesized in good yields by condensation of equimolar amounts of 4-chloro-1,2-cyclohexanedione and 1,3-cyclohexanedione or 5,5-dimethyl-1,3-cyclohexandione via heating under reflux in toluene for 3 hours as the reported method[13,14]. The 4-chloro -1,2-diaminobenzene reacts satisfactorily in this way provided that a 1: 1 molar ratio of the reactants was used where there was no amount of products from two molecules of 1,3-cyclic diketones and one molecule of the respective amine[15] . The structures of the novel enaminones were confirmed using elemental analyses,IR and ^{1}H-NMR spectra . The ^{1}H-NMR spectra showed a singlet at 4.4 ppm for the vinylic proton as well as a singlet at 4.95 ppm integrating two protons of the amino group. In addition the appearance of singlet at 7.9 ppm integrating one proton of the imino group.

The novel nonclassical dibenzodiazepine derivatives (4-29) were prepared via internal Mannich reaction [16-19] by allowing the 3-(2-amino-4- chlorophenyl)amino-2-cyclohexen-1-one (2a) or the 5,5-dimethyl analog (2b) to react at room temperature with different aldehydes in ethanol containing drops of glacial acetic acid as catalyst as shown in scheme (A). The high reactivity of the enaminones (2a and 2b) towards the aldehydes can be attributable to the enaminone structure in which α-position is particularly reactive to electrophilic reagents [16]. The reaction was characterized by being almost quantitative and without by-product (compound 3). The new dibenzodiazepine derivatives were characterized using elemental analyses, IR, ^{1}H-NMR and mass spectroscopic methods. ^{1}H-NMR showed no singlet at 4.4 ppm for the vinylic proton as well as no singlet at 4.95 ppm for the amino group of the starting enaminones. In addition the appearance of very characteristic doublet at 5.45-5.6 ppm integrating one proton of the CH at position 11 as well as a doublet at 6.25- 6.35 integrating one proton of the NH at position 10 of the dibenzodiazepine skeleton.

In conclusion, new nonclassical dibenzodiazepine derivatives were synthesized from easily accessible starting materials with high yields at room temperature . Some compounds showed good antipsychotic and sedative activities with nonsignificant agranulocytosis.

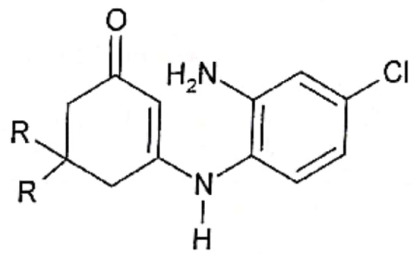
EXPERIMENTAL

All melting points were determined with a Gallenkamp digital melting point apparatus in open capillaries and are uncorrected. Elemental analyses were performed at the microanalytical center, Cairo University, Cario, Egypt. Infrared spectra (cm^{-1}) were run in KBr on Perkin-Elmer FT-IR1650 Spectrophotometer. Mass spectra were determined on Hewlett Packard MS-5988 spectrometer at 70 eV. ^{1}H-NMR spectra were recorded on a Varian EM-390, 90 MHz spectrometer using TMS as an internal standard and DMSO-d_6 as solvent (chemical shift in δ, ppm).

3-[(2-Amino-4-chlorophenyl) amino]-2- cyclohexen -1 - one and its 5,5-dimethyl analog (2a and 2b).

A mixture of equimolar amounts of 1,3 - cyclohexanedione or 5,5-dimethyl -1,3- cyclohexanedione and 4-chloro- 1,2-diaminobenzene (0.02 mol) was heated under reflux in toluene (40 ml) for 3 hours. The reaction mixture was concentrated and then allowed to cool to room temperature. The separated crystalline product was filtered, dried and recrystallized from toluene (Table 1).

Table (1) : Physical data for compounds (2a and 2b).



No.	R	m. p. °C	% yield	M. Formula (M.Wt)	Elemental analyses	Calcd.	Found
2a	H	147-9	86	$C_{12}H_{13}ClN_2O$ (236.67)	C	60.9	60.7
					H	5.5	5.6
					N	11.8	11.6
2b	CH_3	190-2	90	$C_{14}H_{17}ClN_2O$ (264.72)	C	63.5	63.7
					H	6.5	6.4
					N	10.6	10.4

IR: 3480-3400 (asym. and sym NH_2) , 3310 (NH), 3040 (CH aromatic), 2960 (CH aliphatic), 1630 (C=O) .

^{1}H-NMR: compound 2a : δ 1.60 -2.45 (m ,6H, 3x CH_2), 4.4 (s, 1H,CH =C),4.95 (s, 2H, NH_2, D_2O-exchang.), 6.2-7.0 (m, 3H, Ar-H), 7.9 (s,1H, NH, D_2O-exchang.) .

8-Chloro-2,3,4,5,10,11-hexahydro-11-substituted-1H-dibenzo[b,e] [1,4] diazepin-1-ones and their 3,3-dimethyl analogs (4-29)

To a solution of the respective enaminone 2a or 2b (0.0042 mol) in 15 ml ethanol, were added the appropriate aldehyde (0.0042 mol) and 5 drops of glacial acetic acid and the resulting mixture was allowed to stand at room temperature for 3 hours. The separated crystalline product was filtered, dried and recrystallized from the appropriate solvent (Table 2).

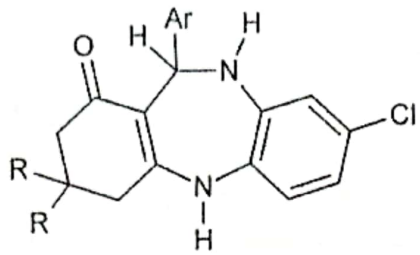
IR: major frequencies: 3750 (br , OH) , 3370 (NH), 3290 (NH), 3100-3050 (CH, aromatic) 2960-2940 (CH, aliphatic), 1610-1590 (conj C=O), 1570-1540 (C=C), 1510 (NO_2), 1340 (NO_2) .

^{1} H-NMR: Compound 6 : δ 1.8 - 2.0 (m, 2H, CH_2), 2.1-2.3 (m, 2H, CH_2), 2.5 -2.7 (m, 2H, CH_2), 5.45 (d, 1H, CH at position 11), 6.25 (d, 1H, NH, at position 10, D_2O-exchang.), 6.4-7.0 (m, 7H, Ar-H), 8.6 (s, 1H, NH, at position 5, D_2O-exchang.) .

Compound 8: δ 1.75-2.0 (m, 2H, CH_2), 2.1 -2.3 (m, 2H, CH_2), 2.6-2.8 (m, 2H, CH_2) 5.7 (t, 2H, CH and NH, D_2O-exchang, at positions 11 and 10, respectively), 6.4 -7.0 (m, 7H,Ar-H), 8.75 (s, 1H, NH, D_2O-exchang.) .

Zagazig J. Pharm. Sci., June 2000
Vol. 9 , No. 1, pp. 9 -16

Table (2) : Physical data for compounds (4-29).



No.	R	Ar	RS[a]	m.p.°C	% yield	M. Formula (M. Wt)	Elemental analyses		
								Calcd.	Found
4	H	4-(Br) C_6H_4-	Dioxane /H_2O	242-4	85	$C_{19}H_{16}BrClN_2O$ (403.66)	C H N	56.5 4.0 6.9	56.3 4.1 6.7
5	H	2-(Cl) C_6H_4-	Ethanol	225-7	82	$C_{19}H_{16}Cl_2N_2O$ (359.21)	C H N	63.5 4.5 7.8	63.3 4.3 7.9
6	H	3-(Cl) C_6H_4-	Ethanol /H_2O	206-8	83	$C_{19}H_{16}Cl_2N_2O$ (359.21)	C H N	63.5 4.5 7.8	63.4 4.3 7.6
7	H	4-(Cl) C_6H_4-	Dioxane /H_2O	237-9	85	$C_{19}H_{16}Cl_2N_2O$ (359.21)	C H N	63.5 4.5 7.8	63.6 4.4 7.9
8	H	2-(F) C_6H_4-	Ethanol	217-9	81	$C_{19}H_{16}ClFN_2O$ (342.75)	C H N	66.6 4.7 8.2	66.4 4.5 8.3
9	H	2-(OH)C_6H_4-	Ethanol	169-71	76	$C_{19}H_{17}ClN_2O_2$ (340.77)	C H N	67.0 5.0 8.2	67.2 5.1 8.0
10	H	4-(OH)C_6H_4-	Ethanol	266-8	78	$C_{19}H_{17}ClN_2O_2$ (340.77)	C H N	67.0 5.0 8.2	67.1 5.2 8.4
11	H	2-(NO_2)C_6H_4-	Dioxane /H_2O	247-9	87	$C_{19}H_{16}ClN_3O_3$ (369.77)	C H N	61.7 4.4 11.4	61.6 4.3 11.6
12	H	4-(NO_2)C_6H_4-	Dioxane /H_2O	250-2	83	$C_{19}H_{16}ClN_3O_3$ (369.77)	C H N	61.7 4.4 11.4	61.9 4.6 11.5
13	H	C_6H_5-	Ethanol	248-50	80	$C_{19}H_{17}ClN_2O$ (324.77)	C H N	70.3 5.7 8.6	70.1 5.2 8.5
14	H	4-(CH_3)$_2$ N C_6 H_4 -	Ethanol /H_2O	239-41	80	$C_{21}H_{22}ClN_3O$ (367.84)	C H N	68.6 6.0 11.4	68.8 6.2 11.6

Cont. Table (2) :

No.	R	Ar	RS[a]	m.p.°C	% yield	M. Formula (M. Wt)	Elemental analyses	Calcd.	Found
15	H	2-Thienyl	Ethanol /H_2O	259-61	79	$C_{17}H_{15}ClN_2OS$ (330.79)	C H N	61.7 4.6 8.5	61.5 4.8 8.7
16	H	4-(CH_3O)C_6H_4-	Ethanol	240-2	78	$C_{20}H_{19}ClN_2O_2$ (354.80)	C H N	67.7 5.4 7.9	67.5 5.6 7.7
17	CH_3	4-(Br)C_6H_4-	Dioxane /H_2O	287-9	90	$C_{21}H_{20}BrClN_2O$ (431.71)	C H N	58.4 4.7 6.5	58.6 4.9 6.7
18	CH_3	2-(Cl)C_6H_4-	Ethanol	256-8	85	$C_{21}H_{20}Cl_2N_2O$ (387.26)	C H N	65.1 5.2 7.2	65.3 5.4 7.4
19	CH_3	3-(Cl)C_6H_4-	Ethanol /H_2O	228-30	84	$C_{21}H_{20}Cl_2N_2O$ (387.26)	C H N	65.1 5.2 7.2	65.2 5.1 7.0
20	CH_3	4-(Cl) C_6H_4-	Ethanol /H_2O	278-80	92	$C_{21}H_{20}Cl_2N_2O$ (387.26)	C H N	65.1 5.2 7.2	65.0 5.0 7.1
21	CH_3	2-(F) C_6H_4 -	Dioxane	227-9	88	$C_{21}H_{20}ClFN_2O$ (370.8)	C H N	68.0 5.4 7.6	68.2 5.2 7.4
22	CH_3	2-(OH)C_6H_4-	Ethanol /H_2O	185-7	85	$C_{21}H_{21}ClN_2O_2$ (368.82)	C H N	68.4 5.7 7.6	68.3 5.9 7.8
23	CH_3	4-(OH)C_6H_4-	Ethanol /H_2O	248-50	87	$C_{21}H_{21}ClN_2O_2$ (368.82)	C H N	68.4 5.7 7.6	68.2 5.8 7.4
24	CH_3	2-(NO_2)C_6H_4-	Dioxane	233-5	89	$C_{21}H_{20}ClN_3O_3$ (397.82)	C H N	63.4 5.1 10.6	63.2 4.9 10.4
25	CH_3	4-(NO_2)C_6H_4-	Ethanol /H_2O	270-2	91	$C_{21}H_{20}ClN_3O_3$ (397.82)	C H N	63.4 5.1 10.6	63.2 4.9 10.8

Cont. Table (2)

No.	R	Ar	RS[a]	m.p.°C	% yield	M. Formula (M. Wt)	Elemental analyses	Calcd.	Found
26	CH_3	C_6H_5-	Ethanol /H_2O	257-9	90	$C_{21}H_{21}ClN_2O$ (352.82)	C H N	71.5 6.0 7.9	71.3 6.2 8.1
27	CH_3	4-$(CH_3)_2NC_6H_4$-	Ethanol /H_2O	187-9	89	$C_{23}H_{26}ClN_3O$ (359.89)	C H N	69.8 6.6 10.6	69.7 6.8 10.8
28	CH_3	2-Thienyl	Ethanol	238-40	91	$C_{19}H_{19}ClN_2OS$ (358.85)	C H N	63.6 5.3 7.8	63.4 5.5 7.9
29	CH_3	4-$(CH_3O)C_6H_4$-	Ethanol /H_2O	218-20	88	$C_{22}H_{23}ClN_2O_2$ (382.85)	C H N	69.0 6.1 7.3	69.2 6.1 7.2

RS[a] = recrystallization solvent

Compound 21 : δ 1.0, 1.1 (two s, 2 x 3H , gem methyl), 2.1 (d, 2H, CH_2 at position 2), 2.6 (s, 2H, CH_2 at position 4), 5.75 (t, 2H, CH and NH,D_2O-exchang. at positions 11 and 10 respectively), 6.4 -7.1 (m, 7H,Ar-H),8.75 (s,1H, NH at position 5, D_2O-exchang.).

Compound 29 : δ 1.05, 1.1 (two s, 2 x 3H, gem methyl), 2.1 (d, 2H, CH_2 at position 2), 2.55 (s, 2H, CH_2 at position 4),3.55 (s,3H, OCH_3), 5.5(d,1H, CH at position 11), 6.2(d, 1H, NH, D_2O-exchang.), 6.40- 6.95 (m, 7H, Ar-H), 8.6 (s, 1H, NH,D_2O-exchang.) .

MS (Compound 5) : m / z (rel. intensity) 359.15 (3.94, M^+), 358.15 (9.97), 323.15 (18.79) , 247 (100) .

Pharmacological studies

The newly synthesized compounds (4, 15 , 17 and 28) were tested for antipsychotic and sedative activities via ptosis and sleeping time tests respectively using clozapine as a refrence drug. In addition, the animals were subjected to leucocytic count to investigate the presence or absence of agranulocytosis which usually induced during the course of treatment with clozapine as a side effect.

(1) Ptosis test :

It was carried out according to the method described by **Chen and Bohner** [20] . Thirty six male albino mice weighing 25-35 g were used. They were divided into 6 equal groups (n=6) . The first group was labelled as control and injected intraperitonealy (i.p.) with the solvent dimethylsulfoxide (DMSO) while the second group was injected (i.p.) with clozapine in a dose of 1.5 mg/kg . The tested compounds (4,15, 17 and 28) were injected (i.p.) to the other groups in a dose of 1.5 mg/kg. Every mouse was observed for the presence or absence of complete ptosis. The ptosis was rated as the fraction of the eyelid closure from normal .

The ptosis ratio was made 4 for complete ptosis, 3 for 3/4 , 2 for 1/2 and one for 1/4 ptosis . Two readings of each mouse were taken and averaged .

(2) Sleeping time test :

The effects of the tested drugs on sleeping time were conducted according to the method described by **Alpermann** [21] . Thirty six adult albino mice weighing 25-35 g of both sex were used . They were divided into 6 equal groups (n=6) . The first group was left as control and injected (i.p.) with the solvent (DMSO) while the second group administered (i.p.) clozapine in a dose of 1.5 mg/kg . The tested compounds (4,15,17 and 28) were injected (i.p.) to the remaining groups in a dose of 1.5 mg/kg . The time from losing to regaining of the righting reflex was determined.

(3) Leucocytic count method:

Thirty six adult mice of both sex weighing 25-35 g were used for white blood cells (WBCs) count .

Mice were divided into 6 groups (n=6) . The first group was left as control and injected (i.p) with the solvent (DMSO) . The second group was injected (i.p) with clozapine in a dose of 1.5 mg/kg / day for three successive days. The tested compounds (4, 15 , 17 and 28) were injected (i.p.) to the other groups in a dose of 1.5 mg / kg / day for three days . Blood samples were collected in tubes containing sodium citrate 3.8% as anticoagulant for haematological studies . Blood

Table (3) : The effect of clozapine and the new chosen compounds (4,15 , 17 and 28) on male mice using ptosis test (n= 6)

Group	Treatment	Ptotic scoring	% effect
1	Control	0 (no ptosis)	0.00
2	Clozapine	3 (3/4 ptosis)	100.0
3	Compound 4	4 (complete ptosis)	133.3
4	Compound 15	2 (1/2 ptosis)	66.60
5	Compound 17	4 (complete ptosis)	133.3
6	Compound 28	2 (1/2 ptosis)	66.60

Table (4) : The effect of intraperitoneal injection of clozapine and the new chosen compounds on the sleeping time of mature mice (n =6)

Group	Treatment	Onset (min)		Sleeping time (min)	
1	Control	0	(0.00)	0	(0.00)
2	Clozapine	8.16±0.38	(100)	32.7±0.41	(100)
3	Compound 4	6.3±0.24***	(77.2)	93.8±0.68***	(286.8)
4	Compound 15	8.0±0.16	(98.0)	27.16±0.37***	(83.2)
5	Compound 17	7.6±0.07	(93.1)	56.6±0.78***	(173.1)
6	Compound 28	15.6±0.15***	(191.2)	25.3±0.22***	(77.4)

*** P< 0.001 Note : values between brackets showing the percentage effect

Table (5) : The effect of clozapine and the new chosen compounds on the leucocytic count ($10^3/mm^3$) n = 6

Group	Treatment	One day post-treatment		Two days post-treatment		one week post-treatment	
1	Control	10.53±0.91	(100)	10.46±0.85	(100)	10.43±0.78	(100)
2	Clozapine	7.38±0.225*	(70.0)	5.63±0.436***	(53.8)	4.02±0.38***	(38.5)
3	Compound 4	9.98±0.138	(94.7)	8.65±0.237	(82.6)	9.8±0.3	(93.9)
4	Compound 15	7.95±0.76	(75.4)	5.1±0.4***	(48.7)	4.1±0.42***	(39.3)
5	Compound 17	9.05±0.464	(85.9)	8.25±0.23	(78.8)	8.8±0.148	(84.4)
6	Compound 28	7.92±0.136*	(75.2)	7.8±0.192*	(74.5)	7.2±0.171*	(69.0)

* P< 0.05 *** P< 0.001 Note : values between brackets showing the percentage effect

1.5 mg / kg / day for three days . Blood samples were collected in tubes containing sodium citrate 3.8% as anticoagulant for haematological studies . Blood samples were collected after one, two and seven days of the last dose in all groups . Total leucocytes were counted according to the method of **Schalm** [22] .

Results of pharmacological studies :

Compound 4 (nonmethylated analog of compound 17):

It showed 33.3% higher antipsychotic activity than clozapine Table (3). The onset of sedation of compound 4 was 6.3 min. which was shorter than that of clozapine by 22.8% . Surprizingly , its duration of action was longer by 186.8% than that of clozapine Table (4) . Luckily, compound 4 showed nonsignificant decrease (6.1% from control) in white blood cells (WBCs) count while clozapine exhibted significant decrease (61.5 % from control) which induces the agranulocytosis after one week post- treatment Table (5) .

Compound 17:

Compound 17 showed 33.3% higher antipsychotic activity than that of clozapine Table (3). These compounds Table (4) can be arranged :

a) According to their onset of sedation into compound 4 (77.2%)< compound 17 (93.1%)< clozapine(100%)
b) According to the duration of their sedative activity into Compound 4 (286.8%)> compound 17 (173.1%) > clozapine (100%).

It is apparent that compounds 4 and 17 have a higher antipsychotic and sedative activities than clozapine due to the presence of 4-bromophenyl moiety in each . Indeed , the halogen substituent in different antipsychotic diarylazepine analogs has been considered as an important structural element in the drug - receptor interaction [23]. Its favourable influence might be related not only to electron - withdrawing effect but also the increased lipophilicity [24]. In addition, the methylated derivative (compound 17) showed a lower sedative effect than the nonmethylated one (compound 4) due to the presence of geminal methyl groups which may affect the planarity of the molecule. Compound 17 showed nonsignificant decrease in leucocytic count by 15.6% from control which is negligible if compared with that of clozapine (61.5%) after one week post - treatment Table (5) .

Compound 15 (nonmethylated analong of compound 28) :

Compound 15 showed moderate antipsychotic activity which represents 33.3% lower than that of clozapine Table (3). Moreover, its onset time of sedation was nearly the same as clozapine while its duration of action is shorter than that of clozapine by 16.8% Table (4). Compound 15 causes significant decrease in leucocytic count by 60.7% which is nearly similar to clozapine after one week post - treatment Table (5) .

Compound 28 :

Compound 28 exhibited 33.3% lower antipsychotic activity than that of clozapine Table (3) .In addition, compound 28 (methylated derivative) showed a lower sedative effect than both clozapine and compound 15 Table (4) . The geminal methyl groups of compound 28 may be responsible for the difference in sedative activity because of their expected effect on the planarity of tricyclic skeleton. Compound 28 also causes neutropenia which was lesser than that of clozapine (31% for compound 28 and 61.5% for clozapine) after one week post- treatment Table (5).

It could be concluded that, both compound 4 and 17 possess greater antipsychotic activity and lesser side effect than that of clozapine. Despite of their greater antipsychotic activity , these compound (4 and 17) may be preferred to be promising as hypnotic compounds. So further pharmacological studies should be carried out to cover this point.

REFRENCES

1- Schmutz, J., **Arzneim. Forsch.** , 25, 712-720 (1975).
2-Ogren, S. O. The behavioral pharmacology of typical and atypical antipsychotic drugs. In handbook of Experimental Pharmacology; Csernansky, J. G.,Ed.; Springer: NewYork, 120, pp 225-226 (1996) .
3-Liegeois, J. F. F.; Bruhwyler, J.; Rogister, F. A and Delarge, J.E., **Curr. Med. Chem.,** 1, 471-501 (1995) .
4-Liegeois , J. F. F.; Bruhwyler, J. ; Damas, J. ; Nguyen, T. P.; Chleide , E. M. G. ; Mercier, M. G. A. ; Rogister, F. A. and Delarge, J. E. , **J. Med. Chem.,** 36, 2107-2114 (1993).
5-Martindale (The Extra Pharmacopoeia), edited by Reynolds, J. E. F. Copyright (c) by the Royal Pharmaceutical Society of Great Britain Published by the pharmaceutical press, London 30 ed. , Vol. 1 p. 583 (1993)
6-Schaus, J. M. and Bymaster, F.P., **Annu. Rep. Med. Chem.,** 33, 1-10 (1998)
7-Meltzer, H.; Matsubara, S. and Lee, J. C., **J. Pharmacol. Exp. Ther.,** 251, 238-246 (1989).
8-Baldessarini, R. and Frankenburg, F.,**N. Engl. J. Med.,** 324, 746-754(1991).
9-Jackson, D. M.; Ryan, C.; Evenden, J. and Mohell, N., **Acta Psychiatry Scand.,** 89, 41-48 (1994).
10-Lieberman, J. A.; Johns, C. A.; Kane, J. M.; Rai, K.; Pisciotta, A. V.; Saltz, B. L. and Howard, A., **J. Clin. Psychiatry** , 49, 271-277 (1988).
11-Casey, D. E., **J. Clin. Psychiatry** , 57, 40-52 (1996).
12- Meier, E. ; Bartoszyk, G. D. ; Böttcher, H. ; Seyfried, C. A. and Sundell, S., **J. Med. Chem.,** 42, 2235-2244 (1999).
13-Edafiogho, I. O.; Hinko, C. N.; Chang, H.; Moore, J. A.; Mulzac, D.; Icholson, J. M. and Scott, K. R., **J. Med Chem.,** 35, 2798 (1992).
14-El-Sabbagh, O. I.; El-Bermawy, M. A.; El-Sadek, M. A. and Al-Ashmawi, M. I.,**Zag. J. Pharm. Sci.,** 3,131 (1994).
15-Greenhill, J. V., **J. Chem. Soc. Perkin I,** 2207 (1976).
16-Greenhill, J. V., **Chem Soc. Rev.,** 6, 277 (1977).
17-Miyano, S. and Abe, N.,**Chem. Pharm. Bull.,** 20, 1588 (1972).
18- Rashed, N.; Sayed, M. and El-Ashry, E. S. H., **J. Chin. Chem. Soc.,** 40, 189 (1993).
19-Vanden Eynde, J. J.; Mayence, A.; Maquestiau, A. and Anders, E., **Bull. Soc. Chim. Belg.,** 101, 801 (1992).
20-Chen, G. and Bohner, B. , Cited in screening methods in pharmacology , Academic Press. New York and London, 1st ed., p. 182 (1965).
21-Alpermann H., Thr. Sabry, M. A. Some Pharmacological Studies On Ketamine HCl and its Interaction with Xylazine. M.V.Sc.Thesis, Faculty of Vet. Medicine, Zagazig Univ., Egypt, pp.73-74 (1981) .
22-Schalm, O. W.; Jam, N. C. and Carroll, E. T. Veterinary Haematology, 3rd ed. Lea and Febiger, Philadelphia (1975).
23-Froimowitz, M. and Ramsby , S., **J. Med. Chem.,** 34, 1707-1714 (1991).
24-Liegeois , J. F. F.; Rogister, F. A ; Bruhwyler, J. ; Damas, J. ; Nguyen, T. P.; Inarejos, M. O.; Chleide , E. M. G. ; Mercier, M. G. A. and Delarge, J. E., **J. Med. Chem.,** 37, 519-525 (1994).

Received : 8 February (2000)
Accepted : 30 March (2000)

Osama I.I.-Sabbagh and Abd-El Alim F. Abd-El Alim

تشييد بعض مشتقات البنزوديازيبين الجديدة والغير تقليدية ذات الفعالية فى علاج الامراض النفسية

أسامه إبراهيم الصباغ وعبد العليم فؤاد عبد العليم*

قسم الكيمياء الطبيه - كليه الصيدله - جامعه الزقازيق - الزقازيق - مصر

* قسم الفارماكولوجى - كليه الطب البيطرى - جامعه الزقازيق - الزقازيق - مصر

يشتمل هذا البحث على تحضير سلسلتين من ٨ - كلور - ٢ ، ٣ ، ٤ ، ٥ ، ١٠ ، ١١ - هكساهيدرو- ١١- مستبدل - ١ يد - داى بنزو{ ب، د} {٤،١} داى أزيبين-١- أون ومراد فتها من ٣،٣ ثنائى المثيل وذلك بتطبيق تفاعل مانيخ الداخلى على كل من ٣ {٢١- أمينو -٤- كلورو فينيل) أمينو } سيكلوهكسين -١- أون ومقابله ٥ ,٥- ثنائى المثيل تباعا مع الألدهيدات المختلفة عند درجه حرارة الغرفه ولقد تم تقييم الخواص العلاجية لهذه المركبات بالمقارنة بمثيلاتها مثل عقار الكلوزابين.

وقد تم إثبات التركيبات البنائية لهذه المركبات الجديدة من خلال التحليل الدقيق للعناصر وكذلك الطرق الطيفية المختلفة وبدراسه الخواص العلاجية لبعضها وجد أن المركبان رقما (٤، ١٧) والمحتويان على مجموعة ٤-بروموفنيل لهما خواص عالية فى علاج الأمراض النفسية وكذلك لهما خواص مهدئة.